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APPL-NO: 08/411,098 DATE FILED: Mar. 27, 1995

L3: 5 of 10

TITLE: Eukaryotic layered vector initiation systems
US PAT NO: 5,814,482 DATE ISSUED: Sep. 29, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/739,158 DATE FILED: Oct. 30, 1996
REL-US-DATA: Division of Ser. No. 404,796, Mar. 15, 1995, which is a continuation-in-part of Ser. No. 376,184, Jan. 18, 1995, abandoned, which is a continuation-in-part of Ser. No. 348,472, Nov. 30, 1994, abandoned, which is a continuation-in-part of Ser. No. 198,450, Feb. 18, 1994, abandoned, which is a continuation-in-part of Ser. No. 122,791, Sep. 15, 1993, abandoned.

L3: 6 of 10

TITLE: Fragments of a lymphocyte adhesion receptor for high endothelium, CD44
US PAT NO: 5,808,004 DATE ISSUED: Sep. 15, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/472,543 DATE FILED: Jun. 7, 1995
REL-US-DATA: Division of Ser. No. 884,624, May 15, 1992, Pat. No. 5,504,194, which is a continuation of Ser. No. 628,646, Dec. 12, 1990, abandoned, which is a division of Ser. No. 325,224, Mar. 17, 1989, Pat. No. 5,002,873.

L3: 7 of 10

TITLE: Alphavirus structural protein expression cassettes
US PAT NO: 5,789,245 DATE ISSUED: Aug. 4, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/741,881 DATE FILED: Oct. 30, 1996
REL-US-DATA: Division of Ser. No. 404,796, Mar. 15, 1995, which is a continuation-in-part of Ser. No. 376,184, Jan. 20, 1995, abandoned, which is a continuation-in-part of Ser. No. 348,472, Nov. 30, 1994, abandoned, which is a continuation-in-part of Ser. No. 198,450, Feb. 18, 1994, abandoned, which is a continuation-in-part of Ser. No. 122,791, Sep. 15, 1993, abandoned.

L3: 8 of 10

TITLE: Diagnostic and therapeutic agents using a lymphocyte adhesion receptor for high endothelium CD44
US PAT NO: 5,770,569 DATE ISSUED: Jun. 23, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/472,542 DATE FILED: Jun. 7, 1995
REL-US-DATA: Division of Ser. No. 884,624, May 15, 1992, Pat. No. 5,504,194, which is a continuation of Ser. No. 628,646, Dec. 12, 1990, abandoned, which is a division of Ser. No. 325,224, Mar. 17, 1989, Pat. No. 5,002,873.

L3: 9 of 10

TITLE: Lymphocyte adhesion receptor for high endothelium, CD44
US PAT NO: 5,504,194 DATE ISSUED: Apr. 2, 1996
[IMAGE AVAILABLE]
APPL-NO: 07/884,624 DATE FILED: May 15, 1992
REL-US-DATA: Continuation of Ser. No. 628,646, Dec. 12, 1990, abandoned, which is a division of Ser. No. 325,224, Mar. 17, 1989, Pat. No. 5,002,873.

L3: 10 of 10

TITLE: DNA sequence encoding a lymphocyte adhesion receptor for high endothelium
US PAT NO: 5,002,873 DATE ISSUED: Mar. 26, 1991
[IMAGE AVAILABLE]
APPL-NO: 07/325,224 DATE FILED: Mar. 17, 1989

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US PAT NO: 5,861,310 [IMAGE AVAILABLE] L3: 1 of 10

ABSTRACT:
Tumor cells modified to express one or more T cell **costimulatory molecules** are disclosed. Preferred **costimulatory molecules** are B7-2 and B7-3. The **tumor** cells of the invention can be modified by **transfection** with nucleic acid encoding B7-2 and/or B7-3, by using an agent which induces or increases expression of B7-2 and/or B7-3 on the **tumor** cell or by coupling B7-2 and/or B7-3 to the **tumor** cell. **Tumor** cells modified to express B7-2 and/or B7-3 can be further modified to express B7. **Tumor** cells further modified to express MHC class I and/or class II **molecules** or in which expression of an MHC associated protein, the invariant chain, is inhibited are also disclosed. The modified **tumor** cells of the invention can be used in methods for treating a patient with a **tumor**, preventing or inhibiting metastatic spread of a **tumor** or preventing or inhibiting recurrence of a **tumor**. A method for specifically inducing a CD4.sup.+ T cell response against a **tumor** and a method for treating a **tumor** by modification of **tumor** cells in vivo are disclosed.

SUMMARY:

BSUM(9)

Accordingly, the invention pertains to methods of inducing or enhancing T lymphocyte-mediated anti-**tumor** immunity in a subject by use of a modified **tumor** cell having increased immunogenicity. In one aspect of the invention, a **tumor** cell is modified to express one or more T cell **costimulatory molecules** on its surface. Preferred **costimulatory molecules** are novel B lymphocyte antigens, B7-2 and B7-3. Prior to modification, the **tumor** cell may lack the ability to express B7-2 and/or B7-3, may be capable of expressing B7-2 and/or B7-3 but fail to do so, or may express insufficient amounts of B7-2 and/or B7-3 to activate T cells. Therefore, a **tumor** cell can be modified by providing B7-2 and/or B7-3 to the **tumor** cell surface, by inducing the expression of B7-2 and/or B7-3 on the **tumor** cell or by increasing the level of expression of B7-2 and/or B7-3 on the **tumor** cell. In one embodiment, the **tumor** cell is modified by **transfecting** the cell with at least one nucleic acid encoding B7-2 and/or B7-3 in a form suitable for expression of the **molecule**(s) on the cell surface. Alternatively, the **tumor** cell is contacted with an agent which induces or increases expression of B7-2 and/or B7-3 on the cell surface. In yet another embodiment, the **tumor** cell is modified by chemically coupling B7-2 and/or B7-3 to the **tumor** cell surface. A **tumor** cell modified to express B7-2 and/or B7-3 can be further modified to express the T cell **costimulatory molecule** B7.

SUMMARY:

BSUM(10)

Even when provided with the ability to trigger a **costimulatory** signal in T cells, modified **tumor** cells may still be incapable of inducing anti-**tumor** T cell-mediated immune responses due to a failure to sufficiently trigger an antigen-specific primary activation signal. This can result from insufficient expression of MHC class I or class II **molecules** on the **tumor** cell surface. Accordingly, this invention encompasses modified **tumor** cells which provide both a T cell **costimulatory** signal and an antigen-specific primary activation signal, via an antigen-MHC complex, to T cells. Prior to modification, a **tumor** cell may lack the ability to express one or more MHC

molecules, may be capable of expressing one or more MHC **molecules** but fail to do so, may express only certain types of MHC **molecules** (e.g., class I but not class II), or may express insufficient amounts of MHC **molecules** to activate T cells. Thus, in one embodiment, a **tumor** cell is modified by providing one or more MHC **molecules** to the **tumor** cell surface, by inducing the expression of one or more MHC **molecules** on the **tumor** cell surface or by increasing the level of expression of one or more MHC **molecules** on the **tumor** cell surface. **Tumor** cells expressing B7-2 and/or B7-3 are further modified, for example, by **transfection** with a nucleic acid encoding one or more MHC **molecules** in a form suitable for expression of the MHC **molecule**(s) on the **tumor** cell surface. Alternatively, such **tumor** cells are modified by contact with an agent which induces or increases expression of one or more MHC **molecules** on the cell.

DETDESC:

DETD(8)

The inability of a **tumor** cell to trigger a **costimulatory** signal in T cells may be due to a lack of expression of a **costimulatory molecule**, failure to express a **costimulatory molecule** even though the **tumor** cell is capable of expressing such a **molecule**, insufficient expression of a **costimulatory molecule** on the **tumor** cell surface or lack of expression of an appropriate **costimulatory molecule** (e.g. expression of B7 but not B7-2 and/or B7-3). Thus, according to one aspect of the invention, a **tumor** cell is modified to express B7-2 and/or B7-3 by **transfection** of the **tumor** cell with a nucleic acid encoding B7-2 and/or B7-3 in a form suitable for expression of B7-2 and/or B7-3 on the **tumor** cell surface. Alternatively, the **tumor** cell is modified by contact with an agent which induces or increases expression of B7-2 and/or B7-3 on the **tumor** cell surface. In yet another embodiment, B7-2 and/or B7-3 is coupled to the surface of the **tumor** cell to produce a modified **tumor** cell.

DETDESC:

DETD(11)

A. **Transfection** of a **Tumor** Cell with a Nucleic Acid Encoding a **Costimulatory Molecule**

DETDESC:

DETD(15)

Alternatively, B7-2 and/or B7-3 can be expressed on a **tumor** cell using a plasmid expression vector which contains nucleic acid, e.g. a cDNA, encoding B7-2 and/or B7-3. Suitable plasmid expression. . . al., EMBO J. 6, 187-195 (1987)). Since only a small fraction of cells (about 1 out of 10.sup.5) typically integrate **transfected** plasmid DNA into their genomes, it is advantageous to **transfect** a nucleic acid encoding a selectable marker into the **tumor** cell along with the nucleic acid(s) of interest. Preferred selectable markers include those which confer resistance to drugs such as. . . on the same plasmid as the gene(s) of interest or may be introduced on a separate plasmid. Following selection of **transfected tumor** cells using the appropriate selectable marker(s), expression of the **costimulatory molecule** on the surface of the **tumor** cell can be confirmed by immunofluorescent staining of the cells. For example, cells may be stained with a fluorescently labeled monoclonal antibody reactive against the **costimulatory molecule** or with a fluorescently labeled soluble receptor which binds the **costimulatory molecule**. Expression of the B7-3 **costimulatory molecule** can be determined using a monoclonal antibody, BB1, which recognizes B7-3. Yokochi, T., et

al. J. Immunol. 128, 823-827 (1982).. . .

DETDESC:

DETD(19)

Another agent which can be used to induce or increase expression of B7-2 and/or B7-3 on a **tumor** cell surface is a nucleic acid encoding a transcription factor which upregulates transcription of the gene encoding the **costimulatory molecule**. This nucleic acid can be **transfected** into the **tumor** cell to cause increased transcription of the **costimulatory molecule** gene, resulting in increased cell-surface levels of the **costimulatory molecule**.

DETDESC:

DETD(24)

Before modification, a **tumor** cell may not express any **costimulatory molecules**, or may express certain **costimulatory molecules** but not others. As described herein, **tumor** cells can be modified by **transfecting** the **tumor** cell with nucleic acid encoding a **costimulatory molecule**(s), by inducing the expression of a **costimulatory molecule**(s) or by coupling a **costimulatory molecule**(s) to the **tumor** cell. For example, a **tumor** cell **transfected** with nucleic acid encoding B7-2 can be further **transfected** with nucleic acid encoding B7. The cDNA sequence and deduced amino acid sequence of human and mouse B7 is shown. . . and SEQ ID NO:7 and 8, respectively. Alternatively, more than one type of modification can be used. For example, a **tumor** cell **transfected** with a nucleic acid encoding B7-2 can be stimulated with an agent which induces expression of B7.

DETDESC:

DETD(26)

Another aspect of this invention features modified **tumor** cells which express a **costimulatory molecule** and which express one or more MHC **molecules** on their surface to trigger both a **costimulatory** signal and a primary, antigen-specific, signal in T cells. Before modification, **tumor** cells may be unable to express MHC **molecules**, may fail to express MHC **molecules** although they are capable of expressing such **molecules**, or may express insufficient amounts of MHC **molecules** on the **tumor** cell surface to cause T cell activation. **Tumor** cells can be modified to express either MHC class I or MHC class II **molecules**, or both. One approach to modifying **tumor** cells to express MHC **molecules** is to **transfect** the **tumor** cell with one or more nucleic acids encoding one or more MHC **molecules**. Alternatively, an agent which induces or increases expression of one or more MHC **molecules** on **tumor** cells can be used to modify **tumor** cells. Inducing or increasing expression of MHC class II **molecules** on a **tumor** cell can be particularly beneficial for activating CD4.sup.+ T cells against the **tumor** since the ability of MHC class II.sup.+ **tumor** cells to directly present **tumor** peptides to CD4.sup.+ T cells bypasses the need for professional MHC class II.sup.+ APCs. This can improve **tumor** immunogenicity because soluble **tumor** antigen (in the form of **tumor** cell debris or secreted protein) may not be available for uptake by professional MHC class II.sup.+ APCs.

DETDESC:

DETD(31)

Fragments, mutants or variants of MHC class II **molecules** that retain

the ability to bind peptide antigens and activate T cell responses, as evidenced by proliferation and/or lymphokine production by T cells, are considered within the scope of the invention. A preferred variant is an MHC class II **molecule** in which the cytoplasmic domain of either one or both of the .alpha. and .beta. chains is truncated. It is known that truncation of the cytoplasmic domains allows peptide binding by and cell surface expression of MHC class II **molecules** but prevents the induction of endogenous B7 expression, which is triggered by an intracellular signal generated by the cytoplasmic domains of the MHC class II protein chains upon crosslinking of cell surface MHC class II **molecules**. Kuolova. L., et al., J. Exp. Med. 173, 759-762 (1991); Nabavi, N., et al. Nature 360, 266-268 (1992). Expression of B7-2 and B7-3 is also induced by crosslinking surface MHC class II **molecules**, and thus truncation of MHC class II **molecules** may also prevent induction of B7-2 and/or B7-3. In **tumor** cells **transfected** to constitutively express B7-2 and/or B7-3, it may be desirable to inhibit the expression of endogenous **costimulatory molecules**, for instance to restrain potential downregulatory feedback mechanisms. **Transfection** of a **tumor** cell with a nucleic acid(s) encoding a cytoplasmic domain-truncated form of MHC class II .alpha. and .beta. chain proteins would. . .

DETDESC:

DETD(56)

The modified **tumor** cells of the present invention can be used to increase **tumor** immunogenicity, and therefore can be used therapeutically for inducing or enhancing T lymphocyte-mediated anti-**tumor** immunity in a subject with a **tumor** or at risk of developing a **tumor**. A method for treating a subject with a **tumor** involves obtaining **tumor** cells from the subject, modifying the **tumor** cells ex vivo to express a T cell **costimulatory molecule**, for example by **transfecting** them with an appropriate nucleic acid, and administering a therapeutically effective dose of the modified **tumor** cells to the subject. Appropriate nucleic acids to be introduced into a **tumor** cell include nucleic acids encoding B7-2 and/or B7-3, alone or together with nucleic acids encoding B7, MHC **molecules** (class I or class II) or Ii antisense sequences as described herein. Alternatively, after **tumor** cells are obtained from a subject, they can be modified ex vivo using an agent which induces or increases expression of B7-2 and/or B7-3 (and possibly also using agent(s) which induce or increase B7 or MHC **molecules**).

US PAT NO: 5,858,776 [IMAGE AVAILABLE] L3: 2 of 10

ABSTRACT:
Tumor cells modified to express a T cell **costimulatory molecule** are disclosed. In one embodiment, the **costimulatory molecule** is a CD28/CTLA4 ligand, preferably a B lymphocyte antigen B7. The **tumor** cells of the invention can be modified by **transfection** with nucleic acid encoding a T cell **costimulatory molecule**, by using an agent which induces or increases expression of a T cell **costimulatory molecule** on the **tumor** cell surface or by coupling a T cell **costimulatory molecule** to the **tumor** cell surface. **Tumor** cells further modified to express MHC class I and/or class II **molecules** or in which expression of an MHC associated protein, the invariant chain, is inhibited are also disclosed. The modified **tumor** cells of the invention can be used in methods for treating a patient with a **tumor**, preventing or inhibiting metastatic spread of a **tumor** or preventing or inhibiting recurrence of a **tumor**. A method for specifically inducing a CD4.sup.+ T cell response against a **tumor** and a method for treating a **tumor** by modification of **tumor** cells in vivo are disclosed.

SUMMARY:

BSUM(9)

Accordingly, the invention pertains to methods of inducing or enhancing T lymphocyte-mediated anti-**tumor** immunity in a subject by use of a modified **tumor** cell having increased immunogenicity. In one aspect of the invention, a **tumor** cell is modified to express a T cell **costimulatory molecule** on its surface. Prior to modification, the **tumor** cell may lack the ability to express a T cell **costimulatory molecule**, may be capable of expressing a T cell **costimulatory molecule** but fail to do so, or may express insufficient amounts of a T cell **costimulatory molecule** to activate T cells. Therefore, a **tumor** cell can be modified by providing a **costimulatory molecule** to the **tumor** cell surface, by inducing the expression of a **costimulatory molecule** on the **tumor** cell surface or by increasing the level of expression of a **costimulatory molecule** on the **tumor** cell surface. In one embodiment, the **tumor** cell is modified by **transfecting** the cell with a nucleic acid encoding a T cell **costimulatory molecule** in a form suitable for expression of the **molecule** on the cell surface. Alternatively, the **tumor** cell is contacted with an agent which induces or increases expression of a T cell **costimulatory molecule** on the cell surface. In yet another embodiment, the **tumor** cell is modified by chemically coupling a T cell **costimulatory molecule** to the **tumor** cell surface.

SUMMARY:

BSUM(11)

Even when provided with the ability to trigger a **costimulatory** signal in T cells, modified **tumor** cells may still be incapable of inducing anti-**tumor** T cell-mediated immune responses due to a failure to sufficiently trigger an antigen-specific primary activation signal. This can result from insufficient expression of MHC class I or class II **molecules** on the **tumor** cell surface. Accordingly, this invention encompasses modified **tumor** cells which provide both a T cell **costimulatory** signal and an antigen-specific primary activation signal, via an antigen-MHC complex, to T cells. Prior to modification, a **tumor** cell may lack the ability to express one or more MHC **molecules**, may be capable of expressing one or more MHC **molecules** but fail to do so, may express only certain types of MHC **molecules** (e.g., class I but not class II), or may express insufficient amounts of MHC **molecules** to activate T cells. Thus, in one embodiment, a **tumor** cell is modified by providing one or more MHC **molecules** to the **tumor** cell surface, by inducing the expression of one or more MHC **molecules** on the **tumor** cell surface or by increasing the level of expression of one or more MHC **molecules** on the **tumor** cell surface. **Tumor** cells expressing a T cell **costimulatory molecule** are further modified, for example, by **transfection** with a nucleic acid encoding one or more MHC **molecules** in a form suitable for expression of the MHC **molecule**(s) on the **tumor** cell surface. Alternatively, such **tumor** cells are modified by contact with an agent which induces or increases expression of one or more MHC **molecules** on the cell.

DETDESC:

DETD(5)

The inability of a **tumor** cell to trigger a **costimulatory** signal in T cells may be due to a lack of expression of a **costimulatory molecule**, failure to express a **costimulatory molecule** even though the **tumor** cell is capable of expressing such a **molecule**, or insufficient expression of a **costimulatory molecule** on the

tumor cell surface. Thus, according to one aspect of the invention, a **tumor** cell is modified to express a **costimulatory molecule** by **transfection** of the **tumor** cell with a nucleic acid encoding a **costimulatory molecule** in a form suitable for expression of the **costimulatory molecule** on the **tumor** cell surface. Alternatively, the **tumor** cell is modified by contact with an agent which induces or increases expression of a **costimulatory molecule** on the **tumor** cell surface. In yet another embodiment, a **costimulatory molecule** is coupled to the surface of the **tumor** cell to produce a modified **tumor** cell. The term "**costimulatory molecule**" is defined herein as a **molecule** which interacts with a T cell which has received a primary activation signal to result in T cell proliferation and/or cytokine production. Preferred **costimulatory molecules** include antigens on the surface of B lymphocytes, professional antigen presenting cells (e.g., monocytes, dendritic cells, Langerhans cells) and other. . . CD28, CTLA4, both CD28 and CTLA4, or other known or as yet undefined receptors on immune cells. A particularly preferred **costimulatory molecule** which binds CD28 and/or CTLA4 is the B lymphocyte antigen B7.

DETDESC:

DETD(8)
A. **Transfection** of a **Tumor** Cell with a Nucleic Acid Encoding a **Costimulatory Molecule**

DETDESC:

DETD(9)

Tumor cells can be modified ex vivo to express a T cell **costimulatory molecule** by **transfection** of isolated **tumor** cells with a nucleic acid encoding a **costimulatory molecule** in a form suitable for expression of the **molecule** on the surface of the **tumor** cell. The terms "**transfection**" or "**transfected** with" refers to the introduction of exogenous nucleic acid into a mammalian cell and encompass a variety of techniques useful. . . acids into mammalian cells including electroporation, calcium-phosphate precipitation, DEAE-dextran treatment, lipofection, microinjection and infection with viral vectors. Suitable methods for **transfecting** mammalian cells can be found in Sambrook et al. (Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory. . . and other laboratory textbooks. The nucleic acid to be introduced can be, for example, DNA encompassing the gene encoding the **costimulatory molecule**, sense strand RNA encoding the **costimulatory molecule** or a recombinant expression vector containing a cDNA encoding the **costimulatory molecule**. Preferred cDNAs to use are those for human and mouse B7 (Freeman, G. J., et al., J Exp. Med 174,. . .

DETDESC:

DETD(12)

Alternatively, a **costimulatory molecule** can be expressed on a **tumor** cell using a plasmid expression vector which contains nucleic acid, e.g. a cDNA, encoding the **costimulatory molecule**. Suitable plasmid expression vectors include CDM8 (Seed, B., Nature 329, 840(1987)) and pMT2PC (Kaufman, et al., EMBO J 6, 187-195 (1987)). Since only a small fraction of cells (about 1 out of 10.sup.5) typically integrate **transfected** plasmid DNA into their genomes, it is advantageous to **transfect** a nucleic acid encoding a selectable marker into the **tumor** cell along with the nucleic acid(s) of interest. Preferred selectable markers include those which confer resistance to drugs such as. . . on the same plasmid as the gene(s) of interest or may be

introduced on a separate plasmid. Following selection of **transfected tumor** cells using the appropriate selectable marker(s), expression of the **costimulatory molecule** on the surface of the **tumor** cell can be confirmed by immunofluorescent staining of the cells. For example, cells may be stained with a fluorescently labeled monoclonal antibody reactive against the **costimulatory molecule** or with a fluorescently labeled soluble receptor which binds the **costimulatory molecule**. Expression of the B7 **costimulatory molecule** can be determined using a monoclonal antibody, 133, which recognizes B7. Freedman, A. S., et al. J Immunol. 139, 3260-3267. . . .

DETDESC:

DETD(13)

When **transfection** of **tumor** cells leads to modification of a large proportion of the **tumor** cells and efficient expression of a **costimulatory molecule** on the surface of **tumor** cells, e.g. when using a viral expression vector, **tumor** cells may be used without further isolation or subcloning. Alternatively, a homogenous population of **transfected tumor** cells can be prepared by isolating a single **transfected tumor** cell by limiting dilution cloning followed by expansion of the single **tumor** cell into a clonal population of cells by standard techniques.

DETDESC:

DETD(16)

Another agent which can be used to induce or increase expression of a **costimulatory molecule** on a **tumor** cell surface is a nucleic acid encoding a transcription factor which upregulates transcription of the gene encoding the **costimulatory molecule**. This nucleic acid can be **transfected** into the **tumor** cell to cause increased transcription of the **costimulatory molecule** gene, resulting in increased cell-surface levels of the **costimulatory molecule**.

DETDESC:

DETD(20)

Another aspect of this invention features modified **tumor** cells which express a **costimulatory molecule** and which express one or more MHC **molecules** on their surface to trigger both a **costimulatory** signal and a primary, antigen-specific, signal in T cells. Before modification, **tumor** cells may be unable to express MHC **molecules**, may fail to express MHC **molecules** although they are capable of expressing such **molecules**, or may express insufficient amounts of MHC **molecules** on the **tumor** cell surface to cause T cell activation. **Tumor** cells can be modified to express either MHC class I or MHC class II **molecules**, or both. One approach to modifying **tumor** cells to express MHC **molecules** is to **transfect** the **tumor** cell with one or more nucleic acids encoding one or more MHC **molecules**. Alternatively, an agent which induces or increases expression of one or more MHC **molecules** on **tumor** cells can be used to modify **tumor** cells. Inducing or increasing expression of MHC class II **molecules** on a **tumor** cell can be particularly beneficial for activating CD4.sup.+ T cells against the **tumor** since the ability of MHC class II.sup.+ **tumor** cells to directly present **tumor** peptides to CD4.sup.+ T cells bypasses the need for professional MHC class II.sup.+ APCs. This can improve **tumor** immunogenicity because soluble **tumor** antigen (in the form of **tumor** cell debris or secreted protein) may not be available for uptake by professional MHC class II.sup.+ APCs.

DETDESC:

DETD(24)

Fragments, mutants or variants of MHC class II **molecules** that retain the ability to bind peptide antigens and activate T cell responses, as evidenced by proliferation and/or lymphokine production by T cells, are considered within the scope of the invention. A preferred variant is an MHC class II **molecule** in which the cytoplasmic domain of either one or both of the .alpha. and .beta. chains is truncated. Truncation of the cytoplasmic domains allows peptide binding by and cell surface expression of MHC class II **molecules** but prevents the induction of endogenous B7 expression, which is triggered by an intracellular signal generated by the cytoplasmic domains of the MHC class II protein chains upon crosslinking of cell surface MHC class II **molecules**. Kuolova. L., et al., J. Exp. Med. 173, 759-762 (1991); Nabavi, N., et al. Nature 360, 266-268 (1992). In **tumor** cells **transfected** to constitutively express B7 or other **costimulatory molecule**, it may be desirable to inhibit the expression of endogenous B7, for instance to restrain potential downregulatory feedback mechanisms. **Transfection** of a **tumor** cell with a nucleic acid(s) encoding a cytoplasmic domain-truncated form of MHC class II .alpha. and .beta. chain proteins would. . .

DETDESC:

DETD(35)

The **tumor** cells to be modified as described herein include **tumor** cells which can be **transfected** or treated by one or more of the approaches encompassed by the present invention to express a **costimulatory molecule**. If necessary, the **tumor** cell can be further modified to express MHC **molecules** or an inhibitor of Ii expression. A **tumor** from which **tumor** cells are obtained can be one that has arisen spontaneously, e.g in a human subject, or may be experimentally derived or induced, e.g. in an animal subject. The **tumor** cells can be obtained, for example, from a solid **tumor** of an organ, such as a **tumor** of the lung, liver, breast, colon, bone etc. Malignancies of solid organs include carcinomas, sarcomas, melanomas and neuroblastomas. The **tumor** cells can also be obtained from a blood-borne (ie. dispersed) malignancy such as a lymphoma, a myeloma or a leukemia.

DETDESC:

DETD(36)

The **tumor** cells to be modified include those that express MHC **molecules** on their cell surface prior to **transfection** and those that express no or low levels of MHC class I and/or class II **molecules**. A minority of normal cell types express MHC class II **molecules**. It is therefore expected that many **tumor** cells will not express MHC class II **molecules** naturally. These **tumors** can be modified to express a **costimulatory molecule** and MHC class II **molecules**. Several types of **tumors** have been found to naturally express surface MHC class II **molecules**, such as melanomas (van Duinen et al., **Cancer** Res. 48, 1019-1025, 1988), diffuse large cell lymphomas (O'Keane et al., **Cancer** 66, 1147-1153, 1990), squamous cell carcinomas of the head and neck (Mattijssen et al., Int. J **Cancer** 6, 95-100, 1991) and colorectal carcinomas (Moller et al., Int. J **Cancer** 6, 155-162, 1991). **Tumor** cells which naturally express class II **molecules** can be modified to express a **costimulatory molecule**, and, in addition, other class II **molecules** which can increase the spectrum of TAA peptides which can be presented by the **tumor** cell. Most non-malignant cell types express MHC class I **molecules**. However, malignant transformation is often accompanied by

downregulation of expression of MHC class I **molecules** on the surface of **tumor** cells. Csiba, A., et al., Brit. J **Cancer** 50, 699-709 (1984). Importantly, loss of expression of MHC class I antigens by **tumor** cells is associated with a greater aggressiveness and/or metastatic potential of the **tumor** cells. Schrier, P. I., et al. Nature 305, 771-775 (1983); Holden, C. A., et al. J Am. Acad. Dermatol. 9., 867-871 (1983); Baniyash, M., et al. J Immunol. 129, 1318-1323 (1982). Types of **tumors** in which MHC class I expression has been shown to be inhibited include melanomas, colorectal carcinomas and squamous cell carcinomas. van Duinen et al., **Cancer** Res. 48, 1019-1025, (1988); Moller et al., Int. J **Cancer** 6, 155-162, (1991); Csiba, A., et al., Brit. J **Cancer** 50, 699-709 (1984); Holden, C. A., et al. J Am. Acad. Dermatol. 9., 867-871 (1983). A **tumor** cell which fails to express class I **molecules** or which expresses only low levels of MHC class I **molecules** can be modified by one or more of the techniques described herein to induce or increase expression of MHC class I **molecules** on the **tumor** cell surface to enhance **tumor** cell immunogenicity.

DETDESC:

DETD(49)

The modified **tumor** cells of the present invention can be used to increase **tumor** immunogenicity, and therefore can be used therapeutically for inducing or enhancing T lymphocyte-mediated anti-**tumor** immunity in a subject with a **tumor** or at risk of developing a **tumor**. A method for treating a subject with a **tumor** involves obtaining **tumor** cells from the subject, modifying the **tumor** cells ex vivo to express a T cell **costimulatory molecule**, for example by **transfecting** them with an appropriate nucleic acid, and administering a therapeutically effective dose of the modified **tumor** cells to the subject. Appropriate nucleic acids to be introduced into a **tumor** cell include a nucleic acid encoding a T cell **costimulatory molecule**, for example a CD28 and/or CTLA4 ligand such as B7, alone or together with nucleic acids encoding MHC **molecules** (class I or class II) or Ii antisense sequences as described herein. Alternatively, after **tumor** cells are obtained from a subject, they can be modified ex vivo using an agent which induces or increases expression of a **costimulatory molecule** (and possibly also using agent(s) which induce or increase MHC **molecules**).

US PAT NO: 5,843,723 [IMAGE AVAILABLE] L3: 3 of 10

DETDESC:

DETD(72)

Another example of an immunomodulatory cofactor is the B7/BB1 **costimulatory** factor. Briefly, activation of the full functional activity of T cells requires two signals. One signal is provided by interaction of the antigen-specific T cell receptor with peptides which are bound to major histocompatibility complex (MHC) **molecules**, and the second signal, referred to as costimulation, is delivered to the T cell by antigen-presenting cells. Briefly, the second signal is required for interleukin-2 (IL-2) production by T cells and appears to involve interaction of the B7/BB1 **molecule** on antigen-presenting cells with CD28 and CTLA-4 receptors on T lymphocytes (Linsley et al., J. Exp. Med., 173:721-730, 1991a, and J. Exp. Med., 174:561-570, 1991). Within one embodiment of the invention, B7/BB1 may be introduced into **tumor** cells in order to cause costimulation of CD8.sup.+ T cells, such that the CD8.sup.+ T cells produce enough IL-2 to expand and become fully activated. These CD8.sup.+ T cells can kill **tumor** cells that are not expressing B7 because costimulation is no longer required for further CTL function. Vectors that express both the **costimulatory** B7/BB1 factor

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and, for example, an immunogenic HBV core protein, may be made utilizing
methods which are described herein. Cells transduced with these
vectors will become more effective antigen-presenting cells. The HBV
core-specific CTL response will be augmented from the fully activated
CD8.sup.+  T cell via the costimulatory ligand B7/BB1.

=> d his

     (FILE 'USPAT' ENTERED AT 17:50:39 ON 24 FEB 1999)
                E KIPPS, THOMAS ?/IN
                E CANTWELL, MARY ?/IN
                E SHARMA, SANJAI ?/IN
L1            6 S E4,E5
L2           61 S (ACCESSORY OR COSTIMULATORY)(P)(MOLECULE?)(P)(TRANSDUC?
OR
L3           10 S L2(P)(TUMOR? OR TUMOUR? OR CANCER)

=> s l2 and (cd40(w)ligand or cd40L or gp39)

           165 CD40
         21239 LIGAND
            71 CD40(W)LIGAND
            20 CD40L
            22 GP39
L4           0 L2 AND (CD40(W)LIGAND OR CD40L OR GP39)

=> s (tranfect? or transduc?)(P)(cd40(w)ligand or cd40L or gp39)

           159 TRANFECT?
         97056 TRANSDUC?
           165 CD40
         21239 LIGAND
            20 CD40L
            22 GP39
L5           3 (TRANFECT? OR TRANSDUC?)(P)(CD40(W)LIGAND OR CD40L OR GP39)

=> d l5 1-3 date


                                                    L5: 1 of 3
TITLE:          TRAF inhibitors
US PAT NO:      5,789,550                 DATE ISSUED:   Aug. 4, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/700,749                DATE FILED:    Aug. 14, 1996

                                                    L5: 2 of 3
TITLE:          Product and process for targeting an immune response
US PAT NO:      5,698,679                 DATE ISSUED:   Dec. 16, 1997
                [IMAGE AVAILABLE]
APPL-NO:        08/309,006                DATE FILED:    Sep. 19, 1994

                                                    L5: 3 of 3
TITLE:          Method of preventing or treating disease characterized by
                  neoplastic cells expressing CD40
US PAT NO:      5,674,492                 DATE ISSUED:   Oct. 7, 1997
                [IMAGE AVAILABLE]
APPL-NO:        08/360,923                DATE FILED:    Dec. 21, 1994
REL-US-DATA:    Continuation-in-part of Ser. No. 172,664, Dec. 23, 1993,
                  abandoned.

=> d l5 1-3 kwic


US PAT NO:      5,789,550 [IMAGE AVAILABLE]             L5: 1 of 3
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DETDESC:

DETD(84)

Compounds . . . agent, would release TRAF from its complexed form. As an example, this compound can be a native ligand the signal **transduction** of which is mediated by TRAF, e.g. TNF, a **CD40 ligand**, a CD30 ligand, etc. The concentration of the free or bound TRAF can then be detected and/or the dissociation constant. . .

US PAT NO: 5,698,679 [IMAGE AVAILABLE] L5: 2 of 3

DETDESC:

DETD(29)

In . . . cause a T cell to be stimulated, anergized or killed. Activation of a T cell refers to induction of signal **transduction** pathways in the T cell resulting in production of cellular products (e.g., interleukin-2) by that T cell. Anergy refers to. . . antigen. Effector molecules involved in T cell activation include, but are not limited to, B7, B7-2, CD28, CD40 and the **CD40 ligand**. APCs having B7 or B7-2, and CD40 are capable of activating T cells by binding to CD28 and **CD40 ligand**, respectively, on the surface of a T cell. Such APCs are referred to as professional APCs. APCs lacking B7 or. . .

US PAT NO: 5,674,492 [IMAGE AVAILABLE] L5: 3 of 3

DETDESC:

DETD(23)

The . . . disclosed herein is a ligand for CD40, a receptor that is a member of the TNF receptor super family. Therefore, **CD40L** is likely to be responsible for **transducing** signal via CD40, which is known to be expressed, for example, by B lymphocytes. Full-length **CD40L** is a membrane-bound polypeptide with an extracellular region at its C terminus, a transmembrane region, and an intracellular region at its N-terminus. A soluble version of **CD40L** can be made from the extracellular region or a fragment thereof and a soluble **CD40L** has been found in culture supernatants from cells that express a membrane-bound version of **CD40L**. The protein sequence of the extracellular region of murine **CD40L** extends from amino acid 47 to amino acid 260 in SEQ ID NO:2 of USSN 07/969,703. The protein sequence of the extracellular region of human **CD40L** extends from amino acid 47 to amino acid 261 in SEQ ID NO:2. The biological activity of **CD40L** is mediated by binding to CD40or a species-specific homolog thereof and comprises proliferation of B cells and induction of immunoglobulin secretion from activated B cells. **CD40L** (including soluble monomeric and oligomeric forms, as well as membrane-bound forms) can effect B cell proliferation and immunoglobulin secretion (except. . .

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=> s (tumor? or tumour? or cancer)(P)(cd40(w)ligand or cd40L or gp39)

         26041 TUMOR?
          2429 TUMOUR?
         26098 CANCER
           165 CD40
         21239 LIGAND
            20 CD40L
            22 GP39
L6          37 (TUMOR? OR TUMOUR? OR CANCER)(P)(CD40(W)LIGAND OR CD40L OR
GP3
               9)
```

The . . . or negative apoptotic signal. For example, physiological stimuli that prevent or inhibit apoptosis include, for example, growth factors, extracellular matrix, **CD40 ligand**, viral gene products neutral amino acids, zinc, estrogen and androgens. In contrast, stimuli which promote apoptosis include growth factors such as **tumor** necrosis factor (TNF), Fas, and **transforming** growth factor .beta. (TGF.beta.), neurotransmitters, growth factor withdrawal, loss of extracellular matrix attachment, intracellular calcium and glucocorticoids, for example. Other. . .

US PAT NO: 5,837,816 [IMAGE AVAILABLE] L7: 2 of 5

DETDESC:

DETD(2)

The present invention relates to a method of preparing a soluble hetero-oligomeric mammalian polypeptide (or protein) by culturing a host cell **transformed** or **transfected** with an expression vector encoding a fusion protein comprising a leucine zipper domain and a heterologous mammalian protein. Preferably, the. . . that act together to bind a ligand (such as IL-2), for example. Exemplary mammalian transmembrane proteins include members of the **tumor** necrosis factor/nerve growth factor receptor (TNFR/NGFR) family (Farrah and Smith, Nature 358:26, 1992; Goodwin et al., Cell 73:447; 1993), which includes **CD40 Ligand** (CD40-L), CD27 Ligand (CD27-L), OX40 Ligand (OX40-L), and TNF. Structural studies of certain members of this family of proteins indicate. . .

US PAT NO: 5,786,173 [IMAGE AVAILABLE] L7: 3 of 5

SUMMARY:

BSUM(5)

The . . . or negative apoptotic signal. For example, physiological stimuli that prevent or inhibit apoptosis include, for example, growth factors, extracellular matrix, **CD40 ligand**, viral gene products neutral amino acids, zinc, estrogen and androgens. In contrast, stimuli which promote apoptosis include growth factors such as **tumor** necrosis factor (TNF), Fas, and **transforming** growth factor .beta. (TGF.beta.), neurotransmitters, growth factor withdrawal, loss of extracellular matrix attachment, intracellular calcium and glucocorticoids, for example. Other. . .

US PAT NO: 5,716,805 [IMAGE AVAILABLE] L7: 4 of 5

DETDESC:

DETD(2)

The present invention relates to a method of preparing a soluble mammalian protein by culturing a host cell **transformed** or **transfected** with an expression vector encoding a fusion protein comprising a zipper domain and a heterologous mammalian protein. In one embodiment,. . . heterologous mammalian protein comprises an extracellular domain of a mammalian transmembrane protein. Exemplary mammalian transmembrane proteins include members of the **tumor** necrosis factor/nerve growth factor receptor (TNFR/NGFR) family (Farrah and Smith, Nature 358:26, 1992; Goodwin et al., Cell 73:447; 1993), which includes **CD40 Ligand** (CD40-L), CD27 Ligand (CD27-L), OX40 Ligand (OX40-L), and TNF. Structural studies of certain members of this family of proteins indicate. . .

US PAT NO: 5,674,492 [IMAGE AVAILABLE] L7: 5 of 5

DETDESC:

DETD(92)

This example illustrates the effect of recombinant human **CD40 ligand** on the growth of human B-cell lymphomas in SCID mice. SCID mice were obtained, and treated substantially as described in Example 4, above. On day 0, SCID mice were injected either intraperitoneally with 5.times.10.sup.6 RL or TU2C cells. The **tumor** cell recipients then received 100 .mu.l of concentrated supernatant fluid from cells **transfected** with either a vector encoding human **CD40 ligand**, or vector alone (control). Two concentrations of the **CD40 ligand**-containing supernatant fluid were tested: a ten-fold concentrate and a two-fold concentrate (10x and 2x, respectively). The concentrated supernatants were administered. . . third day for a period of 15 days (total of 5 injections), starting at day 3. Mice were monitored for **tumor** development and progression; moribund mice were euthanized. All mice were necropsied for evidence of **tumor**. Liver, kidney and lymphoid organs were analyzed histologically for presence of **tumor** cells. Both parametric (student's t test) and non-parametric (Wilcoxan rank sum test) analyses were performed to determine if the groups. . .